dup(3p21→pter). Excluding the three patients with holoprosencephaly, the average age at time of reporting of patients with dup(3p23 or 25→pter) was 6·3 years. The reason for this is unclear since the occurrence of cleft lip and palate, type and severity of cardiac malformations, occurrence of seizures, frequency of gastrointestinal or renal malformations, etc, seems to be fairly uniform in distribution among patients with early death and those with longer survival times.

In summary, dup(3p) does appear to be a recognisable clinical entity. Most are secondary to malsegregation of parental chromosome rearrangements. However, in de novo chromosome rearrangements, the specificity of clinical anomalies and Giemsa banding studies should allow easy identification of affected subjects. Detailed initial reports and extended follow up reporting of these patients may allow further correlation between specific phenotypic features, suggested influence on survival, and duplication of specific chromosome segments.

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Presumptive mosaic origin of an XX/XY female with ambiguous genitalia

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SUMMARY A child with ambiguous genitalia had an XX/XY karyotype in all tissues examined. Analyses of 11 informative polymorphisms, both chromosomal and genetic (Rh and HLA), showed no difference between the two cell lines. It is unlikely that the child originated from fertilisation of the egg and the second polar body by two sperms; therefore, we hypothesise that the child originated from an XXY zygote after mitotic errors during cleavage. Recent findings of differences in the chromosome constitution between the extra-embryonic tissues and the fetus support this view.

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Persons with both 46,XX and 46,XY cell lines have been reported for many years. Race and Sanger[1] and Tippett[2] present an excellent summary of their characteristics including detailed information of individual cases.

There are two main types. One frequently presents with ambiguous genitalia and XX and XY cells are present in blood and other tissues. Analysis of genetic markers shows evidence of two separate and partly complementary contributions by the mother as well as two independent contributions from the father. It is presumed that two separate acts of fertilisation of two distinct haploid products from one oocyte have occurred. Therefore, they have been defined as dispermic or primary chimera.

The other type is invariably associated with twinning. Detection has usually been fortuitous

following investigation of blood groups. Only a single line of cells corresponding to the sex of the subject is found in tissues other than blood. Analysis by genetic markers provides evidence of two independent acts of fertilisation. It is presumed to originate from an exchange of cells between two independent fetuses by mean of placental vascular anastomoses. They are called twin or secondary chimeras.

The possibility that an XX/XY subject may arise as a mosaic from an XXY zygote by two separate non-disjunctional (or lagging) events very early in development (with subsequent disappearance of the original XXY cell line) has been suggested.[3] We give details here of a female child with ambiguous genitalia who is probably an example of this type.

Case report

The proband was the product of a term pregnancy and normal delivery. During the pregnancy, Debendox (dicyclomine with doxylamine and pyridoxine) was given to the mother because of hyperemesis gravidarum. The proband's mother was 19 years old and this was her second pregnancy. Her first child died of asphyxia during premature labour and was reported to be a normal female.

At birth the proband was 52 cm long and weighed 4·150 g; Apgar score at one minute was 8 and at five minutes was 10. The neonatal period was uneventful. Physical examination at eight days of age was normal except for the genitalia; the phallus was 20 mm long and 12 mm in diameter. An empty bifid scrotum or fused outer labia and a urogenital sinus or scrotal hypospadias were noted. A supposed gonad of 1 ml volume was palpable in the left inguinal area. No hyperpigmentation was present. Blood pressure was normal. Serum electrolytes and 17-OH-progesterone levels were repeatedly normal. Basal levels of FSH, LH, DHEA, DHEA-S, 17-β-oestradiol, testosterone, and androstenedione were within normal limits for age. Bone age and chronological age corresponded closely. A laparotomy performed at 45 days showed the presence of a normal uterus, an atrophic gonad (?streak) on the right, and one testicle on the left side.

Histological examination of biopsies from the gonads was consistent with a dysgenetic testis (R) and an immature testis (L). Because of the anatomical findings, it was decided to raise the child as a girl.

At 14 months of age, the proband was again admitted to hospital for bilateral gonadectomy. Clitoral recessing and opening of the vaginal introitus were carried out during the same surgical session. The hormone levels and bone age were still normal.

Histological examination of the removed gonads showed an ovotestis on the right and an immature testis on the left. At a follow up visit at three years, the proband's height was 100 cm (97th centile) and weight 20 kg (above the 97th centile).

Methods

Cultures of peripheral blood lymphocytes and fibroblasts from skin, gonads, and preputium biopsies were carried out using standard techniques. Two subsequent gonadal biopsies were obtained, the first after exploratory laparotomy, the second during genital plastic surgery. A total of 399 cells was examined. Sequential Q and NOR banding was used to detect polymorphic markers in the proband and both her parents.

Red cells of the patient and of her parents were tested at the MRC Blood Group Unit, London. HLA-A, B, and C antigens were assigned in the proband and her parents by the standard lymphocyte microtoxicity assay.

Results

The initial cytogenetic examination showed that both 46,XX and 46,XY cells were present in leucocyte and fibroblast cultures (table 1). Fibroblasts from the

TABLE 1 *Results of chromosome analyses from different tissues of the proband.*

	46,XX	*46,XY*
Blood	73	42
Skin biopsy	11	3
From laparotomy	50	0
Right gonad biopsy		
From genital plastic surgery	41	9
From laparotomy	18	2
Left gonad biopsy		
From genital plastic surgery	41	9
Preputium	10	90

TABLE 2 *Centromeric polymorphism.*

Chromosome	*Mother*	*Father*	*Child*	
			XX cells	*XY cells*
1	ab	ab	ab	ab
3	ab	bc	ac	ac
9	ab	bc	bc	bc
13	ab	cd	bc	bc
14	ab	ac	aa ab	aa ab
15	ab	cd	ad	ad
16	ab	ab	ab	ab
21	ab	cd	ad	ad
22	ab	bc	ac	ac
Total cells	8	10	20	13

The letters a, b, c, and d are adopted formally to designate clearly identifiable differences, whatever their nature, following Jacobs and Morton.[4]

TABLE 3 *Rh antigen and genotype.*

Subject	*Antigen*	*Genotype*
Father	R_1r	CDe/cde or CDe/cDe or cDe/Cde
Mother	R_1R_1	CDe/CDe or CDe/Cde
Child	R_1R_1	CDe/CDe or CDe/Cde

TABLE 4 *HLA specificities.*

Subject	*Specificities identified*
Father	A9;B12;Cw4/B5
Mother	A2/B13
Child	A9;B12;Cw4/B13

left gonad (at re-examination after three months of continuous culturing of the transplanted fragments) showed only the XY complement in all 20 cells examined. Analysis of the centromere associated marker features of chomosomes 1, 3, 9, 13, 14, 15, 16, 21, and 22 indicated that, although there were clear differences between the father and mother, the two cell lines of the child were apparently identical. Examinations were carried out by two independent observers. All karyotypes were identified by number and scored blind. Polymorphism was assessed by relative differences in size, shape, and brightness. The results are summarised in table 2.

In the blood groups, out of 11 systems tested, only Rh proved to be informative (table 3). HLA results are given in table 4.

Discussion

Studies of genetic and chromosome markers in XX/XY persons with no history of twinning indicate that in the great majority they are the result of fertilisation by two sperms of two maternal nuclei.[2] Nevertheless, there are some cases in which the analysis of polymorphic markers failed to show any difference in the two lines,[5–7] suggesting a single gametic contribution from each parent.

THE EXCLUSION OF CHIMERISM

The origin of the two cell lines through dispermic chimerism cannot be absolutely excluded in our case. However, the probability of the child being such a chimera can be calculated from the marker data. For this calculation we assume a normal first division of the oocyte with extrusion of the first polar body, followed by 'immediate cleavage' and fertilisation of the two products (second polar body and egg pronucleus) by two independent spermatozoa. Assuming that recombination of the markers with the centromeres is very low,[8] if it occurs at all, it can be assumed that the marker is firmly linked to the centromere of the chromosome it marks. Thus, the set of markers contributed by the mother to the two distinct zygotes will be identical. Each spermatozoon will have an equal chance of carrying either one or the other of each pair of homologues. Therefore, the chance of each of the zygotes receiving an equal contribution (the same marker chromosome) from both sperms instead of two different contributions will be 1/2.

Table 2 shows that the XX and XY cell lines of the child received the same marker chromosomes from the father in all the nine instances where an alternative was possible. This sets the combined chance of drawing the same chromosomes in all nine instances at $(1/2)^9$ or 1 in 512.

Regarding the Rh antigen, it is clear from table 3 that, the mother being CC, she could only have transmitted antigen C to her child whereas the father (Cc) could have transmitted either C or c. The probability that the proband received, as in fact occurred, an equal contribution from both sperms (CC or cc) instead of two different contributions (Cc) is therefore 1/2.

HLA specificities (table 4) provide the final evidence. The paternal haplotypes are likely to be equally transmitted by independent spermatozoa. Only one paternal haplotype was detected in the child (though technically both could have been detected if present). The probability of identity is once more 1/2.

Assessment of the maternal contribution is more complicated. The genes of the HLA complex lie approximately in the middle of the short arm of chromosome 6. It is known that recombination within this segment is rare, but the frequency of recombination of the whole segment with the centromere of chromosome 6 is unknown. In the male, there is commonly a single chiasma in the short arm of chromosome 6 bivalent at diakinesis.[8] Recombination in the female, however, is considerably greater.[9] A conservative estimate of a minimal distance of 25 cM between the centromere of chromosome 6 and the HLA segment would mean one crossover dyad entering a secondary oocyte nucleus for every non-crossover dyad. In the model under discussion, a non-crossover dyad would contribute identical haplotypes to the zygotes, whereas the crossover dyad would contribute different haplotypes. The probability of identity of the maternal contribution is then 1/2.

Combining all the probabilities, we have $(1/2)^9$ for certain marker features $\times$ 1/2 for Rh blood group antigen $\times$ 1/2 for male HLA haplotype $\times$ 1/2 for female HLA haplotype = $(1/2)^{12}$= approximately 1:4000. This is the combined chance of observing the

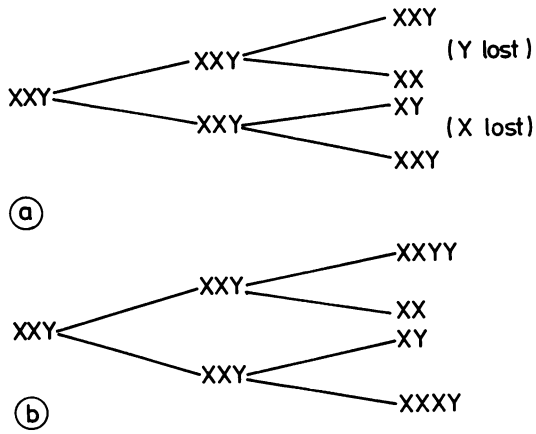

FIGURE *Two different origins of an XX/XY (a) through lagging and (b) through non-disjunction.*

identity of all markers if the child is a chimera and not a mosaic.

EARLY EMBRYOLOGY AND MOSAICISM

Before drawing a final conclusion we examined the plausibility of a mosaic origin in the early embryo. The two most economical hypotheses are shown in the figure.

An XXY zygote is postulated. Clearly, both XX and XY cell lines could not originate before the second cleavage division. Other hypotheses involving lagging or non-disjunction or both at later divisions of the embryo are also possible, but none would yield a cell population in which more than 50% of the cells were of the two types, XX and XY, unless, of course, differential proliferation of cells with different karyotypes occurred. We prefer to avoid such an assumption although it would favour our case.

Current views on the early embryology of both mouse and man are that only three or four cells in a mammalian blastocyst are selected as progenitors of the embryo proper.[10] Thus it seems likely that precocious non-disjunctional events could produce karyotypically distinct lines present in the placenta or in the fetus but not necessarily in both. Demonstration of this can be seen in the papers of Kalousek and Dill[11] and Simoni *et al*,[12] who found examples in man of chromosomal abnormalities confined to extraembryonic tissues. On the basis of the analyses of chromosomal polymorphisms and genetic markers, we therefore conclude that our XX/XY case is a mosaic rather than a chimera.

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Clinical manifestations of trisomy 5q

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SUMMARY A patient with a small deletion of the short arm and a partial duplication of the long arm of chromosome 5 is described. The main clinical features include craniofacial dysmorphism, growth failure, developmental retardation, and congenital heart defect. The

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